This Month in Genetics

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X-Linked Mutations in Male Fetuses Cause Polyhydramnios

There are many causes of polyhydramnios, or excess amniotic fluid, during pregnancy. One is Bartter's syndrome, in which defects in the renal tubules of the fetus are responsible. Bartter's syndrome is also associated with prematurity and with fetal polyuria that continues postnatally in conjunction with salt wasting. In some rare cases, this polyuria and salt wasting are transient, and the babies go on to be perfectly normal. Noticing that the babies with this transient form of disease were all male, Laghmani et al. sought rare variation in X-linked genes as a cause. They uncovered mutations in *MAGED2* in multiple families affected by transient Bartter's syndrome and in some affected by idiopathic polyhydramnios. The genotype of the fetus is what matters; in one case, the affected boy had a de novo nonsense variant in *MAGED2*. Defects in the encoded protein, the melanoma-associated antigen D2, alter expression of the sodium transporter NKCC2 and the sodium chloride cotransporter NCC, thus explaining the salt wasting. The exact function of MAGE-D2 and the explanation for the transience of this salt wasting remain unclear.

Laghmani et al. (2016). Polyhydramnios, transient antenatal Bartter's syndrome, and MAGED2 mutations. New Engl. J. Med. 374, *1853–1863.*

Pinpointing a Culprit in Smith-Lemli-Opitz Syndrome

Although the wide-ranging phenotype and molecular etiology of Smith-Lemli-Opitz syndrome (SLOS) are well documented, the pathophysiology of this cholesterol-biosynthesis disorder is not fully understood. Central to unraveling this mystery is pinpointing the key culprit for each aspect of the phenotype, which could involve either the deficiency of cholesterol, which is downstream of the defective enzyme in SLOS, or the accumulation of its precursor 7-dehydrocholesterol (7DHC). To untangle the two in the context of the neurodevelopmental aspects of SLOS, Francis et al. derived induced pluripotent stem cells (iPSCs) from individuals with SLOS and documented the impact when cells were differentiated into a neural lineage. Compared to control cells, the SLOS iPSCs had precocious neuronal differentiation and loss of pluripotency. These findings were not recapitulated by cholesterol synthesis inhibitors that do not yield 7DHC accumulation, thus pointing the finger at 7DHC in the neurodevelopmental aspects of SLOS. Gene expression signatures in the differentiating SLOS iPSCs implicated the Wnt/β-catenin pathway as an accomplice in the aberrant process, circumstantial evidence that was supported by experiments showing that stabilization of β-catenin prevents the loss of pluripotency.

Francis et al. (2016). Modeling Smith-Lemli-Opitz syndrome with induced pluripotent stem cells reveals a causal role for Wnt/β-catenin defects in neuronal cholesterol synthesis phenotypes. Nature Med. 22, *388–396.*

Epigenetic Variation Influences Metabolic Disease Risk

Mounting evidence suggests that parental metabolic status influences the risk of metabolic disease in children. This influence could operate via genetic or epigenetic mechanisms or via the metabolic conditions during fetal development. To tease out these possibilities, Huypens et al. fed mice a high-fat diet to make them obese, used their sperm or eggs to generate embryos via in vitro fertilization, and implanted the early embryos into non-obese mothers. In a parent-of-origin- and sex-specific manner, the offspring in these experiments were more susceptible to diet-induced obesity and glucose intolerance than were the offspring of mice fed normal chow. Because there was no genetic variation in these experiments and because the embryos were transplanted into non-obese mothers, these findings support the role of epigenetic variation in the influence of parental metabolic status on offspring.

Huypens et al. (2016). Epigenetic germline inheritance of diet-induced obesity and insulin resistance. Nature Genet. 48, *497–499.*

Lamin Mutations Impact Epigenetics

The nuclear lamins are scaffolding proteins that bolster the nuclear envelope. New data from Perovanovic et al. suggests that these proteins are not just structural but impact epigenetic gene regulation too. Variation in the encoding gene, *LMNA*, can cause several different phenotypes, one of which is Emery-Dreifuss muscular dystrophy (EDMD). How variation in a ubiquitously expressed gene has a

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phenotype limited to muscle is not clear. Perovanovic et al. show that EMD-related pathogenic variation in *LMNA* is associated with a drastic increase in the number of genomic loci associated with the nuclear lamina, and these lamin-associated domains are enriched for heterochromatic marks. This impacts myogenesis by altering expression of genes involved in processes central to myogenic differentiation.

Perovanovic et al. Laminopathies disrupt epigenomic developmental programs and cell fate. Sci. Trans. Med. 8, *335ra58.*

Mutational History from Fertilization to iPSCs

Although in clinical genetics we sometimes think of the constitutional genome as being a static entity throughout the body, somatic mutation certainly occurs. Mutation also happens when cells are cultured, and the artificial conditions could cause shifts in mutation accumulation compared to what occurs naturally in the body. To get a better picture of mutation rates in vivo and in culture, Rouhani sequenced genomes of monoclonal cell populations ascertained from individuals. They then derived induced pluripotent stem cells (iPSCs) from the cultures and again sequenced the genomes. Identification of variants that were found across cultures and those that were unique helped them to pinpoint where mutations occurred. Opposite to what I expected, mutation rates in the iPSCs were 10-fold lower than in the somatic cultures; the iPSCs also have a mutational signature that is dominated by oxidative damage, rather than the deamination of methylcytosine, which is the driving force in vivo.

Rouhani et al. Mutational history of a human cell lineage from somatic to induced pluripotent stem cells. PLOS Genet. 12, *e1005932.*

This Month in Our Sister Journal

Neanderthal Fitness

Genetic analyses of ancient samples have given us insight into Neanderthals and uncovered evidence that Neanderthals mixed with humans outside of Africa. Prior to this mixing, inbreeding within the Neaderthal population led to an accumulation of deleterious mutations, which reduced the fitness of this group, compared to humans. Harris and Nielsen used simulations to better understand the ramifications of this admixture between humans and a less fit population. Introduction of genetic variation from Neanderthals probably reduced the fitness of non-African humans with whom the Neanderthals mixed, a finding that is important in explorations of African versus non-African mutation load, especially given that the magnitude of this effect is estimated to be similar to the impact of the out-of-Africa bottleneck. These simulations also help to explain the depletion of Neanderthal-derived haplotypes around functional genomic regions, a phenomenon that has previously been explained by harmful epistatic interactions.

Harris and Nielsen. (2016). The genetic cost of Neanderthal introgression. Genetics Early Online, published April 2, 2016. http://dx.doi.org/10.1534/genetics.116.186890